[thereof] of methoxy(polyethylene glycol).

In claim 10, line 1: delete "pharmaceutical."

Please add to the claims:

11. The monovalent antibody fragment of claim 1, wherein the antigen-binding fragment is selected from the group consisting of an Fab fragment and an Fab' fragment.

Remarks

Preliminarily, Applicants note that a Brief Description of the Drawings and an Abstract are required. The Abstract is enclosed herein. The Brief Description of the Drawings and Abstract have been added to the specification by amendment.

Claims 2-4 and 6-8 have been cancelled and claims 1, 5, 9 and 10 have been amended. The amended claim 1 additionally recites the limitations found in claims 2 and 4. These cancellations and amendment is done without prejudice and the Applicants reserve the right to pursue the subject matter of any of the amended or cancelled claims in a continuing application.

35 USC § 112, ¶ 2

The Examiner has rejected claims 1-10 under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 1 has been rejected as allegedly indefinite in view of the recitation of "modified." The Examiner contends that it is not known what modifications are allowed or contemplated. Claim 1 has been amended to recite "a polymer-modified monovalent antibody fragment." This rejection has been obviated by amendment.

Claims 4 and 5 have been rejected as allegedly indefinite for reciting "derivatives thereof." The Examiner contends that the meaning of "derivative" is not universally accepted in the art and therefore its exact meaning in unknown. The term "derivatives" is defined in the specification (page 6, line 26) as including reactive derivatives, for example, thiol-selective reactive groups such as maleimides. The Applicants submit that it is clear to one of ordinary skill in the art what is meant by derivatives in the present claims.

Claims 3, 4 and 5 have been rejected as allegedly indefinite in reciting the term "optionally." The Examiner contends that it is not clear what options are encompassed by the term. Claim 1 has been amended to recite the limitations of claim 4. Claim 1 now recites "wherein said polymer is an optionally substituted, straight or branched chain polymer selected from the group consisting of..." It is clear in the amended claim 1 that "optionally substituted" modifies polymer. Claims 3 and 4 have been cancelled and rejections to these claims are therefore moot. Claim 5 is dependent on claim 1 does not itself contain the term "optionally." Any rejection to claim 5 in connection with the term "optionally" should therefore removed with the similar rejection of claim 1.

Claims 3, 4 and 5 have been rejected as allegedly indefinite as being structured as improper Markush groups. Claim 5 has been amended to recite "the polymer is selected from the group consisting of methoxy(polyethylene glycol) and derivatives of

methoxy(polyethylene glycol)." Claims 3 and 4 have been cancelled rendering rejections to these claims moot.

Claim 6 has been rejected as allegedly indefinite for reciting "associated." Claim 6 has been cancelled rendering this rejection moot.

Claim 7 has been rejected as allegedly indefinite for reciting "and/or." Claim 7 has been cancelled rendering this rejection moot.

35 USC § 112, ¶ 1

Claim 10 has been rejected under 35 U.S.C. §112, first paragraph as the specification allegedly does not enable a pharmaceutical composition comprising a monovalent antibody together with one or more pharmaceutically acceptable excipients, diluent or carriers. In particularly, the Examiner contends that the enablement of a "pharmaceutical composition" rests on a teaching of *in vivo* administration for purposes consistent with the intended use disclosed in the specification, i.e. the treatment of disease. Applicants direct the Examiner to, *inter alia*, page 18, lines 6-27, and Table 2 of the application as originally filed wherein the pharmokinetics of the fragments according to the invention in rats is described. Additionally, on page 11, lines 22-23, the use of the fragments in the "detection" or treatment of disease is described. Nonetheless, in an effort to advance prosecution, claim 10 has been amended to recite "a composition" rather than "a pharmaceutical composition." Applicants have made this amendment without prejudice. The scope of amended claim 10 includes any composition including "pharmaceutical" compositions.

Claims 1-7 and 9-10 have been rejected under 35 U.S.C. §112, first paragraph, because

the specification allegedly does not reasonably provide support for "antibody fragments." The Examiner acknowledges, however, that the specification is enabling for antigen-binding fragments and Fab and Fab' fragments. Claim 1 has been amended to recite "an antigen-binding fragment." Dependent claim 11 has been added that recites the limitation that the antigen-binding fragment is a Fab or Fab' fragment. Claims 2-4 and 6-7 have been cancelled rendering rejections to these claims moot. Claims 5, 9 and 10 are dependent on claim 1 and therefore contain the limitation of "an antigen-binding fragment" recited in claim 1.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 112 be withdrawn.

35 U.S.C. § 102

Claims 1-10 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Pedley et al. In order for a reference to anticipate the invention, the reference must disclose each and every element of the invention. Pedley et al. teach the covalent attachment of poly(ethylene glycol) (PEG) to IgG, $F(ab')_2$ and Fab' fragments of the anti-CEA antibody. The PEG molecules in Pedley are covalently linked to antibody molecules by conjugating a maleimide-containing derivative of PEG to thiol groups created on the protein using 2-iminothiolane (Traut's reagent) (Pedley, page 1129, column 1). The Traut's reagent is used to replace amine groups with thiol groups. Pedley therefore teaches the random attachment of PEG to residues other than cysteine, anywhere in the antibody fragments. Respectfully, the Examiner is mistaken and Pedley does not teach the selective modification of cysteine residues with PEG.

Claim 1 as amended recites an antigen binding fragment wherein each cysteine molecule located outside the variable region is either covalently linked to a polymer through its sulfur atom, or is in disulfide linkage with a second cysteine located in the antigen binding fragment. The invention therefore has site-specific modification of the antigen binding fragment in selected cysteines outside the variable region. The present invention is therefore distinct from disclosure of the Pedley reference in that the present invention utilizes (1) site-specific modification of (2) cysteines (3) in the nonvariable region of the antigen binding fragment while Pedley teaches (1) random modification of (2) amine groups (3) throughout the antibody fragment.

The random attachment of PEG to amino acid residues is known to result in partial impairment of the function of the protein, i.e. reduced catalytic activity (specification page 2, lines 16-24). Random attachment of PEG to antibodies may lead to reduced affinity, avidity or specificity (specification, page 3, line 7-12). Antigen-binding fragments of the invention in which PEG has been specifically bonded to cysteine residues are disclosed in the present application as retaining more immunoreactivity than randomly PEG-modified Fab' fragments (Table 1). Furthermore, the *in vivo* clearance of the specifically PEG-modified Fab' fragments of the invention was slower than that of randomly PEG-modified Fab' fragments (Fig. 2).

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be withdrawn.

For the foregoing reasons, Applicants submit that the present claims meet all the requirements for patentability. The Examiner is respectfully requested to allow all the present claims. If the Examiner is of a contrary view, it is requested that he contact the undersigned at (215)568-3100.

Respectfully submitted,

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ABSTRACT

Monovalent Antibody fragments are described, each of which has one or more polymer molecules site-specifically attached through a sulphur atom of a cysteine residue located outside of the variable region domain of the antibody. The polymers include synthetic or naturally occurring polymers such as polyalkylenes, polyoxyalkylenes or polysaccharides. Each fragment may be attached to one or more effector or reporter molecules, and is of use in therapy or diagnostics where it has markedly improved binding and/or pharmacokinetic properties when compared to other antibody fragements which have the same number and type of polymer molecules, but in which the polymer molecules are randomly attached.